Factual understanding of randomized clinical trials: a multicenter case-control study in cancer patients

Tanguy Leroy · Véronique Christophe · Nicolas Penel · Pascal Antoine · Stéphanie Clisant

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Summary Objective Several reports have shown that despite the informed consent process, enrolled patients misunderstand the modalities and goals of randomized clinical trials (RCTs). We believe that this may be linked to a priori misconceptions in the main population. The purpose of this study is to compare the knowledge about cancer RCTs in enrolled participants (cases) versus patients treated under cancer standard care who have never taken part in RCTs (controls).

Methods We submitted a validated questionnaire (ICEC-R) to both populations to explore their knowledge about RCTs. A total of 75 cases and 107 controls were included.

Results Globally, the cases’ knowledge was significantly better, especially about (i) the randomization process, (ii) the uncertain potential benefits, and (iii) the right to withdraw consent. Both populations presented the lowest scores for items exploring the randomization process and uncertain treatment benefits.

Conclusion Enrolled patients’ comprehension of the goals and means of RCTs is actually better than controls’. Nevertheless, additional efforts should be made to enhance information about clinical research to patients as well as to the main population.

Practice Implications Having better knowledge about patients’ difficulties in understanding RCTs would allow physicians to adjust the information they give and then to enhance patients’ well-being.

Keywords Cancer · Factual understanding · Information · Informed consent process · Randomized clinical trial

Introduction

The randomized clinical trial (RCT) is the widely acknowledged design of choice for evaluating new therapeutic strategies, especially in cancer care. Obtaining informed consent from patients is the cornerstone of the ethical responsibilities of investigators. It requires that the risk/benefit ratio and alternatives are provided to patients, especially through communication with the physician [1]. The three commonly recognized central elements of the informed consent process are basically (i) adequate disclosure of information to patients regarding a proposed clinical trial, (ii) ensuring that patients understand the information, and (iii) having the patients consent voluntarily to the proposed clinical trial. The difficult question is, how much information is adequate and how does one ensure the patient’s understanding? Not only is enhancing the informed consent process quality crucial for ethical reasons, it could be a determinant for inclusion rates improvement in RCTs as well, and then for therapeutic progress promotion.

Most of the information concerning a clinical trial is disclosed by physicians in a face-to-face dialogue with patients and via a formal informed consent form. However, despite verbal and written explanations, several studies have demonstrated that 40% to 75% of the patients included in randomized Phase III clinical trials may not fully understand these informed consent forms [2–7]. In fact, 30% of the information given to included patients seems to be misunderstood.

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2 h after the informed consent form is signed (40%, 3 months later) [8]. Patients’ misunderstanding of RCTs almost always concerns the randomization process [3] as well as the modalities and even the goals of the RCT.

First, a large part of these deficits in understanding the clinical trial could be directly due to the complexity [9–13] and the length [11] of the informed consent forms, which may interfere with the informed consent process instead of enhancing it. We believe that such hindrances may also be due to (or intensified by) patients’ pre-existing and possibly inaccurate knowledge and representations about clinical research, which would disturb proper information processing. To date, we failed to find data estimating pre-existing knowledge concerning clinical research in people who have never been exposed to such a situation.

Moreover, data dealing with the efficiency of the informed consent process usually focus on patients’ deficits in understanding the goals and modalities of RCTs. The actual benefits of the informed consent process on patients’ factual comprehension of the situation have not yet been clearly assessed. Indeed, to estimate these benefits would require comparing the knowledge about RCTs in patients who have never been explicitly told about clinical research to the knowledge of patients who have been enrolled in an RCT and who have already signed an informed consent form.

Assessing patients’ understanding of the modalities and goals of an RCT remains a major issue concerning ethics and the quality of clinical investigation. Regarding this questionable issue, we conducted a cross-sectional study, using a validated questionnaire, to estimate the factual understanding of cancer RCTs in participating patients (cases) and to compare it to the RCT knowledge of patients treated under standard cancer care who have never taken part in clinical research (controls).

Materials and methods

Patients: cases and controls

All the cancer patients who were already included—for the first time—and who were still being treated in an RCT (Phase II or Phase III study evaluating different chemotherapy regimens or strategies) from May 2006 to June 2007 were eligible to be included in the present study as a “case”, regardless of gender, age, primary tumor location or intent of treatment (palliative versus curative treatment). Likewise, the “controls” were any patients treated by standard care during the same period who had never been included in any clinical trial. Cases and controls were enrolled at Oscar Lambret Cancer Centre, University Hospital of Lille and Hospital of Valenciennes, three medical hospital centers located in Northern France.

Ethics committee

This study has been authorized by the 4th Northern People Protection Committee, the independent decision-making service that northern clinical research units depend on. All patients were explained the aims and the modalities of the study by a psychologist. Finally, 75 out of the 89 contacted case patients (84.3%) and 107 out of the 132 contacted control patients (81.1%) agreed to take part in this study. All the participants (cases and controls) signed a specific informed consent form to be enrolled in our study.

Methods

All the patients (cases and controls) filled out the Understanding RCTs Questionnaire (ICEC-R) [14]. This validated self-assessing questionnaire consists of ten positive statements dealing with four important issues on information usually disclosed to people during the informed consent process: relevant legislation, uncertainty regarding treatment outcomes, randomization and conditions of withdrawal of consent. These statements are generically written in such a way that they never refer either to the patient’s treatment or to any specific RCT: they are either true or false for every RCT, regardless of its actual specific goals or modalities. Patients were asked to indicate whether, in their opinion, each statement was true or false. When in doubt, or when they could not understand the statement, they were encouraged to tick the answer “I don’t know”. Patients’ score of factual comprehension (or knowledge) is equal to the number of correct answers: the higher this score, the better the patients’ understanding.

Statistical analyses

The statistical comparison of obtained scores (good responses) or percentages used were expressed in values according to the Student t-test and the Fischer exact test, respectively. The statistical significance was set at 5%.

Results

Study population

A total of 182 patients suffering from cancer participated in this study (Table 1). The sample comprised 99 males and 83 females from 18 to 84 years of age (mean—M=53.2; standard deviation—SD=13.1); of these, 75 were cases and 107 were controls. There was no statistical difference between the two groups in terms of age, gender and tumor locations, except that lung cancer was more predominant in cases and leukemia was more prevalent in controls.
Overall comprehension score

As expected, the mean score of the ICEC-R was higher in cases ($M=6.43; SD=2.55$) than in controls ($M=4.68; SD=2.33; p<.001$). Modal and median scores were equal to 7 for cases compared to 4 in controls.

Abstention

For each item and for each group, we first focused on the proportion of patients who chose the answer “I don’t know”. In all items, these scores were higher in controls ($M=29.5; SD=5.9$) than in cases ($M=20.7; SD=7.7; p<.05$). Moreover, the proportion of abstention was significantly lower in cases compared to controls for Items 1, 2, 5 and 9. This reduction of abstention in cases is related to a higher proportion of correct answers (Table 2).

Proportion of correct answers for each item

To further investigate patients’ difficulties in understanding the goals and modalities of RCTs, we restricted analyses to “true” and “false” responses. These analyses were conducted so as to highlight patients’ misinterpretations of the information they are given. With this restriction, the proportion of correct answers was above 60% for every statement, excluding Items 6, 9, and 10 (Fig. 1). Furthermore, cases and controls had comparable proportions of correct answers for Items 1, 2, 4 and 6; but cases gave significantly fewer incorrect responses than controls to the six other items (Fig. 1).

Discussion and conclusion

Discussion

We conducted a cross-sectional study to measure the understanding of information disclosed to patients participating in RCTs. We compared the understanding of patients currently included (cases) to the knowledge of controls (cancer patients who have never been recruited for an RCT) via a validated questionnaire (ICEC-R) [14]. The mean

Table 1 Characteristics of cases ($n=75$) and controls ($n=107$)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean &amp; interval)</strong></td>
<td>54.7 [28-82]</td>
<td>52.1 [18-84]</td>
</tr>
<tr>
<td><strong>Sex (number of patients &amp; %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>54.7%</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>45.3%</td>
</tr>
<tr>
<td><strong>Tumor location (number of patients &amp; %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
<td>14.7%</td>
</tr>
<tr>
<td>Urogenital</td>
<td>12</td>
<td>16.0%</td>
</tr>
<tr>
<td>Lung</td>
<td>18</td>
<td>24.0%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>13</td>
<td>17.3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Digestive</td>
<td>15</td>
<td>20.0%</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

Table 2 For each item and for each group of patients, percentages of correct responses (CR), incorrect responses (IR) and abstention (A)

<table>
<thead>
<tr>
<th>Items</th>
<th>Controls ($n=107$)</th>
<th>Cases ($n=75$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>IR</td>
</tr>
<tr>
<td><strong>Relevant legislation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Anonymity of collected data</td>
<td>66.4</td>
<td>4.6</td>
</tr>
<tr>
<td>4. Existence of legislation concerning clinical trials</td>
<td>72.9</td>
<td>1.9</td>
</tr>
<tr>
<td>8. Physicians’ duty to tell their patients everything about the trial</td>
<td>44.9</td>
<td>29.9</td>
</tr>
<tr>
<td><strong>Conditions of trial withdraw</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Right to abort the trial in case of toxicity</td>
<td>73.8</td>
<td>5.6</td>
</tr>
<tr>
<td>5. Right to withdraw from the trial without giving any reason</td>
<td>38.3</td>
<td>21.5</td>
</tr>
<tr>
<td>7. Withdrawing from the trial does not jeopardize the quality of medical care</td>
<td>40.6</td>
<td>31.1</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. All the patients do not receive the same treatment</td>
<td>56.1</td>
<td>17.7</td>
</tr>
<tr>
<td>9. Allocation of treatment at random</td>
<td>12.1</td>
<td>50.5</td>
</tr>
<tr>
<td><strong>Uncertainty regarding treatment outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Uncertainty toward eventual adverse events during the trial</td>
<td>43.0</td>
<td>24.3</td>
</tr>
<tr>
<td>10. Uncertainty about treatment benefits</td>
<td>20.7</td>
<td>49.1</td>
</tr>
</tbody>
</table>
score obtained by cases was significantly higher than that of controls. The cases’ understanding was significantly superior concerning the following issues: (i) the randomization process, (ii) the uncertainty in regards to potential benefits, (iii) the right to withdraw consent without any detrimental impact on continued access to healthcare. However, we have observed that scores were lower in both populations for the items exploring the uncertainty of treatment benefits and the randomization process.

Broadly speaking, the factual understanding of the modalities of RCTs is good in currently included patients. Our results are comparable to those that Bergler et al. reported [8] and are more optimistic than other observations [7, 15]. More precisely, as expected, these patients have a better knowledge of RCTs than patients who have never been told about clinical trials. This difference is characterized by an increased capacity to answer questions about the goals and modalities of an RCT and an increased quality in these answers. These results confirm the primary positive impact of information disclosed to patients during enrolment in an RCT as a way to clarify the conditions of this situation despite the complexity of such information [9–13].

The present study confirms the misunderstanding of “randomization” [3, 16] even if this concept was clearer for cases than controls (52 versus 12%). Uncertainty of clinical benefits is not clearly understood among cases (37%) or among controls (20%). This result confirms the impact of “therapeutic misconception”: participants usually believe that the RCT is conducted for their own personal benefit rather than for more general purposes [17]. That leads them to misunderstand the real potential benefits and risks of the treatment for themselves [15]. Several factors have been found to be correlated with the therapeutic misconception in previous studies: socio-economic characteristics of participants, disease characteristics and the time and the quality of the disclosed information [6, 18]. Moreover, the way informed consent forms are written has to be improved upon so as to make information about these issues more explicit for patients who are involved in an RCT [9–13]. Surprisingly, despite the complexity of informed consent documents and the numerous references to the underlying laws, both cases and controls make the same range of mistakes about the issue of protection of participants and the regulations currently in force; indeed, one quarter of them can not say whether RCTs are regulated by law or not.

This study had several limitations. First of all, this was a multi-centre study conducted in Northern France. The results must be carefully extrapolated to other locations and settings. We do not possess socioeconomic or ethnic data concerning the participants of this research, but it is obvious that further studies should assess the links between such variables and patients’ factual comprehension of the given information. Moreover, some previous studies were aimed at developing a standardized assessment tool to measure the understanding of patients who are recruited for an RCT [5, 15]. Nevertheless, there is no widely accepted method for measuring the results of the informed consent process. Since research questions, procedures and risks vary

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*Fig. 1* Comparison of the percentage of correct responses for each item between cases and controls (*p*<.05; **p**<.01; ***p***<.001)
from one RCT to the next, the tool that is used must be specifically tailored to the types of studies and the types of participants. We focused our study on RCTs (Phases II and III) and used a questionnaire tailored to RCTs in cancer research. This study analyzed the consequences of the whole inclusion process, including the face-to-face dialogue between physicians and patients, the information component that represents the informed consent form and other additional information potentially given by patient associations, research nurses or other caregivers. Here, we provide an evaluation of the results of this global process. Measuring the impacts of each of the sources of information on patients’ understanding of RCTs seems to be quite impossible. At least, it would be necessary to conduct a prospective study allowing taking several measures of patients’ knowledge concerning RCTs during the informed consent process. In particular, measuring a baseline of cases’ knowledge about RCTs would inform us about two possible biases of the present study. First, all patients (cases and controls) signed an informed consent form to take part in this study, which may have modified their knowledge about clinical research and might have reduced intergroup differences. Measuring cases’ baseline and comparing it to their score after the informed consent process would tell us about the factual impact of information given on this occasion. Second, one can imagine that patients who agree to take part to an RCT have more precise a priori representations of clinical trials than other patients, which would directly or indirectly explain the fact that they actually take part in a clinical study. Once again, measuring cases’ baseline would inform about a priori differences between cases and controls. However, measuring such a baseline on the occasion of a prospective study rouses serious ethical concerns in that it may have underestimated consequences on the normal course of patient recruitment in clinical trials.

This study constitutes a first step towards improving our knowledge about patients’ understanding of the modalities and goals of their participation in RCTs. Indeed, most reports on RCTs focus on issues concerning design, methods and results; the patient’s perspective is relatively neglected. However, in order to enhance patient care needs, future investigators have to assess the patients’ factual understanding as well as the way that they believe they understand the conditions.

Conclusion

We have observed that being enrolled in an RCT indeed improves cases’ factual understanding about this specific situation: their knowledge is better than controls’. In addition, we observed that some information is difficult to understand for all the patients, even after the informed consent process, especially that concerning the randomization process and the uncertainty of treatment benefits. This last result leads us to conclude that additional efforts remain to be supplied to improve the way these issues are explained to patients. Misconceptions about RCTs have been observed in controls as well, which indicates that the promotion of clinical research in the main population also remains to be enhanced. Finally, additional studies should be conducted to improve our knowledge of patients’ understanding of the goals and means of RCTs.

Practice implications

From a clinical point of view, further investigations would allow physicians to adjust the information they give to their patients on the basis of the difficulties of assessed factual and perceived understanding. Exploring what intrinsic or extrinsic factors affect the patients’ cognitive processing of information remains a determinant issue for improving patient care. In this manner, physicians would be able to reduce patients’ anxiety regarding the conditions set forth in RCTs and thus, promote their patients’ psychological and emotional adaptation, their well-being and their quality of life.

At the very least, gaining precise knowledge about patients’ understanding would allow sponsors to improve the way informed consent forms are written [9–13]. Efforts are particularly necessary to better explain randomization and the uncertainties regarding risks and benefits. We have observed that deficits in patients’ comprehension may be linked to a priori misconceptions of RCTs in the main population. Indeed, our results confirm that cancer patients do have representations of RCTs even when they are not explicitly given information about clinical studies. This a priori knowledge can either be true or false, depending on individual differences in learning history. Control patients’ scores are actually the lowest when they are questioned about allocation of treatment at random or about the benefits of treatments for RCTs patients, a fact that reveals the existence of misleading conceptions in control patients concerning the goals and the means of clinical research. This misleading a priori knowledge about RCTs may be responsible for cases’ difficulties in efficiently processing informed consent forms as well as information they are given by physicians. That would explain cases’ lower scores for items precisely exploring the randomization process and the expected treatment benefits. One future challenge for physicians and pharmacists may then be to enhance clinical research promotion in the main population so as to enhance people’s knowledge about goals and means of medical research and, as a consequence, to potentially improve patients’ understanding of clinical studies they take part in as well as inclusion rates in RCTs.
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